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Improved insulin sensitivity after a single bout of exercise is curvilinearly related to exercise energy expenditure

Faidon Magkos*[†], Yannis Tsekouras[†], Stavros A. Kavouras[†], Bettina Mittendorfer* and Labros S. Sidossis[†]

* Center for Human Nutrition, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

[†] Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

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Correspondence: Labros S. Sidossis, Ph.D.
Laboratory of Nutrition and Clinical Dietetics
Department of Nutrition and Dietetics
Harokopio University
70 El. Venizelou Avenue
17671 Athens, Greece
Phone: + 30 210 9549 154
Fax: + 30 210 9549 141
E-mail: lsidossis@hua.gr

Abstract

A single bout of moderate-intensity exercise increases whole-body insulin sensitivity for 12-48 hours post-exercise. However, the relationship between exercise energy expenditure and the improvement in insulin sensitivity is not known. We hypothesized that the exercise-induced increase in whole-body insulin sensitivity, assessed with the homeostasis model assessment of insulin resistance (HOMA_{IR}), is directly related to the energy expended during exercise. We studied 30 recreationally active, non-obese men (age: 27 ± 5 years, body mass index: 24 ± 2 kg/m²) in the post-absorptive state on two separate occasions: once after exercising at 60% of peak oxygen consumption for 30-120 min on the preceding afternoon (expending a total of 1.28-5.76 MJ) and once after an equivalent period of rest; blood samples were obtained the following morning. Exercise-induced changes in HOMA_{IR} were curvilinearly related to exercise energy expenditure ($r = -0.666$, $P = 0.001$) with a threshold of ~ 3.77 MJ (900 kcal) for improvements in HOMA_{IR} to manifest. In particular, HOMA_{IR} was reduced by $32 \pm 24\%$ ($P = 0.003$) in subjects who expended more than 3.77 MJ during exercise, but did not change for those who expended fewer than 3.77 MJ ($-2 \pm 21\%$, $P = 0.301$). Furthermore, the magnitude of change in HOMA_{IR} after exercise was directly associated with baseline (i.e., resting) HOMA_{IR} ($r = -0.508$, $P = 0.004$); this relationship persisted in multivariate analysis. We conclude that improved whole-body insulin resistance after a single bout of exercise is curvilinearly related to exercise energy expenditure, and requires unfeasible amounts of exercise for most sedentary individuals.

Introduction

Regular, moderate-intensity, endurance-type physical activity is associated with significantly reduced risk for type 2 diabetes and cardiovascular disease, in part due to enhanced insulin action [1]. Whole-body insulin sensitivity is higher in trained athletes than in untrained subjects, and improves considerably with exercise training in previously sedentary individuals [2]. Most of the enhancement in insulin action associated with exercise training is attributed to the last bout of exercise, and is lost after 3-6 days of inactivity [2-5]. In fact, insulin-mediated whole-body glucose uptake is increased 12-48 hours after a single exercise session in both healthy [6-9] and insulin-resistant subjects [8,10,11] but returns to baseline values thereafter [2-5].

The amount of exercise required to elicit an enhancement in insulin sensitivity remains uncertain. Furthermore, there is considerable inter-individual variability in the metabolic response to acute exercise and the concomitant changes in glucose and insulin dynamics [12], some of which may be related to baseline insulin resistance [10,11,13]. Understanding the dose-response nature of these relationships will have important physiological and public health implications. Current public guidelines advocate 30-60 minutes of moderate-intensity exercise on most days of the week [1]; however, ~70% of the adult population fails to meet the recommended 30-min goal of regular exercise and ~40% does not engage in any kind of physical activity [14]. It was therefore our objective to examine the relationship between the energy expended during exercise and basal whole-body insulin sensitivity, assessed by using the homeostasis model assessment of insulin resistance (HOMA_{IR}), in healthy untrained men.

Methods

25 *Subjects and preliminary testing*

Thirty non-obese, recreationally active but untrained men participated in the study (Table 1). All subjects engaged in moderate-intensity physical activities ≤ 2 times per week, and were

considered to be in good health after completing a medical evaluation, which included a history and physical examination and standard blood tests. None were smoking or taking medications. Body composition (fat mass and fat-free mass) was determined by dual-energy X-ray absorptiometry (Delphi-W, Hologic, Waltham, MA / DPX-MD+, Lunar, Madison, WI), and peak
5 oxygen consumption (VO_{2peak}) was measured with an incremental exercise test on a treadmill (SensorMedics, Vmax229, Yorba Linda, CA) or a cycloergometer (TrueOne 2400, ParvoMedics, Salt Lake City, UT), depending on whether subjects were assigned to perform running or cycling exercise (see *Experimental protocol*). Written informed consent was obtained from all subjects before participation in the study, which was approved by the Human Studies Committee and the
10 General Clinical Research Center Advisory Committee at Washington University School of Medicine in St. Louis, MO, and the Bioethics Committee of Harokopio University, Athens, Greece.

Experimental protocol

15 Each subject completed two studies within three weeks, in randomized order: once after resting and once after exercising on the preceding afternoon. Subjects were instructed to adhere to their regular diet and to refrain from exercise for a minimum of 3 days before the start of each study (rest and exercise). For the exercise study, they came in the laboratory and cycled on a semi-recumbent cycloergometer (Cateye Fitness, Dallas, TX) or ran on a motor-driven treadmill
20 (Technogym Runrace, Italy) at 60% of their VO_{2peak} for 30 to 120 min between 1730-1930 h (7 subjects exercised for 30 min; 7 for 60 min; 9 for 90 min, and 7 for 120 min). There were no significant differences in VO_{2peak} between individuals who exercised for different amounts of time (3.3 ± 0.8 , 3.2 ± 0.6 , 3.3 ± 0.7 and 3.2 ± 0.5 l/min, respectively; $P = 0.883$ by one-way analysis of variance). Oxygen consumption was measured at regular intervals during exercise
25 (every 5, 15, or 30 min, depending on the duration of exercise) to calculate total energy expenditure of the bout (range: 1.28-5.76 MJ, i.e., 306-1376 kcal) [15] and adjust the workload, if necessary, to maintain the desired VO_2 within $\pm 5\%$. The different modes and durations of exercise were chosen in order to cover the range from the minimum recommended amount of exercise (i.e., 30 min of moderate-intensity) [1] to an exercise session that most untrained

individuals would find it difficult to complete (i.e., 2 h in duration) [16], and ensured that the experimental conditions would closely reflect a realistic situation, in which unaccustomed individuals engage in various activities for variable amounts of time. Subjects were not allowed access to any kind of food or beverage during exercise, other than water. For the resting study, subjects lied in bed or sat in a chair. After completion of the exercise or the equivalent period of rest, they consumed the same standardized meal (12 kcal per kg body weight; 50-55% carbohydrate, 30-35% fat and 15-20% protein) at ~2000 h, in order to eliminate between-trial differences in energy balance other than the energy deficit incurred by exercise, and then fasted (except for water) until completion of the study the next day.

At 0800 h the following morning, an arterialized blood sample was obtained from a heated forearm vein for the determination of basal plasma glucose and insulin concentrations. Blood was collected in chilled tubes containing heparin (for glucose) or sodium EDTA plus aprotinin (for insulin) and placed immediately on ice. Plasma was separated by centrifugation within 30 min of collection, and samples were stored at -80°C until analysis. Plasma glucose concentration was determined by the glucose oxidase method on an automated glucose analyzer (YSI 2300 STAT+, Yellow Spring Instruments, Yellow Springs, OH). Plasma insulin concentration was measured by radioimmunoassay (Linco Research, St. Louis, MO). The HOMA_{IR} score, which reflects whole-body insulin resistance, was calculated as the product of fasting plasma insulin (in mU/l) and glucose (in mmol/l) concentrations divided by 22.5 [17].

20

Statistical analysis

Data were analyzed with SPSS 13 for Windows (SPSS Inc, Chicago, IL). All data sets were normally distributed according to the Kolmogorov-Smirnov procedure. Data are presented as means ± standard deviations (SD). Results after rest and after exercise were compared with Student's paired, two-tailed *t* test. Relationships between variables of interest were examined with correlation and regression analyses. *P* < 0.05 was considered statistically significant.

Results

Fasting plasma glucose and insulin concentrations, and therefore the HOMA_{IR} score, were significantly lower the morning after exercise than rest (Table 2). There responses varied
 5 considerably between individuals (Table 2), but were not affected by the mode of exercise (running or cycling) in any consistent manner (not shown).

Total energy expenditure during exercise correlated negatively with exercise-induced changes in fasting plasma glucose ($r = -0.482$, $P = 0.007$) and insulin ($r = -0.521$, $P = 0.003$) concentrations.

There was a negative, curvilinear relationship between total energy expenditure during exercise
 10 and changes in HOMA_{IR} score, with no apparent effect of exercise below a caloric expenditure of ~ 3.77 MJ (i.e., 900 kcal) ($r = -0.666$, $P = 0.001$; Figure 1). Hence HOMA_{IR} was reduced by $\sim 30\%$ in subjects who expended more than 3.77 MJ during exercise ($n = 12$, $P = 0.003$), but did not change for those who expended fewer than 3.77 MJ ($n = 18$, $P = 0.301$; Figure 1). There were no significant differences in subject characteristics between these two groups (Table 1).

15 The relationship between changes in HOMA_{IR} score and exercise energy expenditure was linear when the latter was expressed relative to body weight ($r = -0.577$, $P = 0.001$). However, the percent of variance explained by this linear relationship ($R^2 = 33.3\%$) was less than that explained by the curvilinear relationship with total energy expenditure of exercise ($R^2 = 44.4\%$).

20 The magnitude of change in HOMA_{IR} after exercise was inversely correlated with baseline (i.e., resting) HOMA_{IR} score ($r = -0.508$, $P = 0.004$; Figure 2).

In multivariate linear regression analysis, including exercise energy expenditure, age, body mass index, body weight, fat mass and fat-free mass, VO_{2peak} , and baseline (i.e., resting) plasma glucose and insulin concentrations and HOMA_{IR} score, total energy expenditure during exercise (standardized $\beta = -0.494$, $P = 0.001$) and baseline HOMA_{IR} score ($\beta = -0.420$, $P = 0.005$) were
 25 the only significant independent predictors of the exercise-induced change in HOMA_{IR}, accounting for 49.4% of the total variance ($F = 13.2$, $P < 0.001$).

Discussion

We investigated the relationship between the energy expended during a single bout of moderate-intensity endurance exercise, performed in the evening, and fasting plasma glucose and insulin concentrations and insulin resistance (HOMA_{IR}) the following morning in healthy, non-obese, untrained men. Our findings suggest that improvements in whole-body insulin sensitivity, reflected by decreased HOMA_{IR} score, are curvilinearly related to exercise energy expenditure with a threshold of ~3.77 MJ (900 kcal) for a beneficial effect to manifest. However, exercise-mediated changes in whole-body insulin resistance are inversely related to baseline HOMA_{IR} score, even within this group of normoglycaemic and normoinsulinaemic subjects with normal HOMA_{IR} [18], implying that insulin-resistant individuals may benefit more from exercise than insulin-sensitive ones. Nonetheless, single sessions of typical recreational activities are unlikely to have a significant impact on whole-body insulin sensitivity in healthy sedentary individuals.

It is well established that a single session of strenuous exercise leads to increased insulin-mediated whole-body glucose uptake for some 12-48 hours post-exercise in healthy and insulin-resistant subjects [6-8,10,11]. In our study, whole-body insulin sensitivity improved proportionally with the energy expended during exercise when this exceeded ~3.77 MJ, whereas no changes in HOMA_{IR} score occurred after a total energy cost of exercise less than 3.77 MJ (900 kcal). This energy expenditure threshold is equivalent to ≥60-90 min of exercise at 60% of VO_{2peak} in our recreationally active men, which by far exceeds current public recommendations for physical activity [1]. In fact, most sedentary individuals will probably not be able to exercise for more than 1 hour at this intensity [16]. The existence of an energy expenditure threshold in the insulin-sensitizing effect of exercise is in line with findings on other physiological outcomes of acute exercise, e.g., the lowering of plasma triglyceride concentrations [19,20]. Our findings also help explain the lack of a consistent effect of exercise on insulin sensitivity in some previous studies, because too little exercise was performed (corresponding to total caloric expenditures ≤2.1 MJ or 500 kcal) [13,21]. These results collectively suggest that improvements in basal whole-body insulin sensitivity after a single bout of exercise require unfeasible amounts of exercise for most untrained individuals.

It is possible that regular exercise training lowers the threshold of exercise required to improve whole-body insulin sensitivity; the effects of acute exercise on insulin action appear to be more pronounced in the trained state [2] and every-day, leisure-time physical activity is associated with dose-dependent reductions in diabetes risk in epidemiological surveys [22-25]. However, whether exercise training or the intensity of exercise modify in any way the dose-response relationship between energy expenditure and insulin sensitivity remains to be determined. Furthermore, the inverse association between exercise-induced changes in HOMA_{IR} and baseline HOMA_{IR} implies that less exercise may be required to improve insulin sensitivity in insulin-resistant subjects than those with good insulin sensitivity at baseline, i.e., before engaging in exercise. For instance, some of our subjects with higher baseline HOMA_{IR} scores, albeit within the normal range [18], exhibited large improvements in insulin resistance (i.e., ~20-40% reduction) after expending only 1.26-2.51 MJ (i.e., 300-600 kcal) during exercise. Likewise, insulin-mediated whole-body glucose disposal increased to a greater extent in insulin-resistant obese than in insulin-sensitive lean subjects ~12 hours after a strenuous session of exercise [10], and HOMA_{IR} decreased the morning after a single, 90-min exercise bout at 60% of VO_{2peak} in men but not in women, whose baseline HOMA_{IR} was half that of men [26]. Regular exercise, even of low energy cost, should therefore not be rejected as a means to improve insulin sensitivity in insulin-resistant subjects.

The exact cellular mechanisms responsible for the increase in insulin sensitivity late into recovery from a single bout of exercise are not well understood. Exercise-induced changes in insulin sensitivity have been linked to the depletion of skeletal muscle glycogen and/or triglyceride stores [27]. Depletion of muscle glycogen [6-8,10,11] leads to enhanced post-exercise uptake of glucose to facilitate glycogen replenishment [2,3,28]. The major cellular event underlying this phenomenon is increased translocation of the GLUT4 isoform of glucose transporter from its intracellular storage sites to the cell surface [29]; however, the mechanism(s) responsible for mediating this event, the signals involved, and the amount of exercise required to elicit these signals remain poorly defined [28]. Glycogen repletion in the recovery from exercise occurs in two distinct phases: an early, insulin-independent period of rapid glycogen resynthesis (lasting ~1 hour after cessation of exercise), and a subsequent period (up to 1-2 days post-exercise) of slow glycogen resynthesis which is insulin-dependent [30]. This mechanism fits well with the results from our study, in which muscle glycogen stores were probably not depleted

to any significant extent, except for those subjects who exercised for ≥ 60 -90 min and expended more than ~ 3.77 MJ (900 kcal), as skeletal muscle glycogen is reduced dose-dependently with the total energy cost and hence the duration of exercise [30,31]. We are not aware of any studies examining the possible dose-dependency of exercise-induced changes in relevant signaling pathways. Furthermore, glycogen resynthesis rates are substantially slower in insulin-resistant than insulin-sensitive subjects in the late post-exercise period [32], which could help explain our observation that relatively insulin-resistant subjects (as indicated by higher baseline HOMA_{IR} scores) enjoyed greater decreases in HOMA_{IR} after exercise than relatively insulin-sensitive ones, because persistence of low glycogen stores augments the exercise-induced enhancement in muscle insulin action [28]. Intramuscular triglyceride content is also closely associated with insulin sensitivity [33]. Diminution of skeletal muscle lipid stores and/or enhanced lipid oxidation after exercise could therefore also facilitate muscle insulin action [34]. The relative contribution of changes in skeletal muscle glycogen and triglyceride metabolism to the exercise-induced improvements in insulin sensitivity and the role, if any, of the energy expenditure of exercise are currently not known.

In summary, we investigated the relationship between the total energy expended during a single bout of moderate-intensity evening exercise and changes in fasting plasma glucose and insulin concentrations and HOMA_{IR} in healthy, non-obese, untrained men. Our results indicate that more than 1 hour of moderate-intensity exercise is required to improve basal whole-body insulin sensitivity, assessed with the HOMA_{IR} score. Whether the same applies for repeated exercise sessions (i.e., training) remains to be studied. Although interpretation of our findings is limited by the use of HOMA_{IR} as a surrogate index of whole-body insulin resistance, there is a good correlation ($r = 0.7$ - 0.9) between HOMA_{IR} and estimates of insulin sensitivity derived from hyperinsulinaemic-euglycemic clamp and minimal model analysis [35]. These findings may therefore be useful for the development of appropriate exercise protocols targeted at ameliorating insulin resistance.

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Figure Legends

Figure 1 Exercise-induced changes in homeostasis model assessment of insulin resistance (HOMA_{IR}) as a function of total energy expenditure during exercise (*a*), and for subjects who expended fewer or more than 3.8 MJ (900 kcal) during the exercise bout (*b*; values are means \pm SD; * $P < 0.05$ versus rest).

Figure 2 Exercise-induced changes in homeostasis model assessment of insulin resistance (HOMA_{IR}) as a function of baseline (i.e., resting) HOMA_{IR} score.

Table 1 Subject characteristics

		All subjects	Exercise energy expenditure	
			<3.77 MJ (900 kcal)	>3.77 MJ (900 kcal)
<i>N</i>		30	18	12
Age	(years)	27 ± 5	27 ± 5	27 ± 4
Body mass index	(kg/m ²)	24 ± 2	24 ± 2	24 ± 3
Weight	(kg)	79 ± 11	77 ± 7	82 ± 15
Body fat	(% body weight)	17 ± 4	17 ± 4	17 ± 5
Fat-free mass	(kg)	63 ± 8	61 ± 6	66 ± 9
Peak oxygen consumption (VO _{2peak})	(l/min)	3.3 ± 0.7	3.2 ± 0.7	3.4 ± 0.6
Oxygen consumption during exercise	(l/min)	2.0 ± 0.3	1.9 ± 0.3	2.0 ± 0.3
	(% VO _{2peak})	62 ± 2	61 ± 2	63 ± 2
Total energy expenditure during exercise	(MJ)	3.23 ± 1.40	2.25 ± 0.80	4.69 ± 0.56*
	(kcal)	771 ± 336	537 ± 190	1121 ± 134*

Values are means ± SD.

* $P < 0.001$ vs. corresponding value in subjects who expended less than 3.77 MJ (900 kcal) during exercise.

Table 2 Fasting plasma glucose and insulin concentrations and HOMA_{IR} score after a single evening exercise bout or an equivalent period of rest

		Rest	Exercise	Exercise-induced change (%)	<i>P</i> value
Glucose	(mmol/l)	5.3 ± 0.4	5.1 ± 0.4	-3 ± 6	0.005
Insulin	(mU/l)	6.5 ± 2.6	5.4 ± 2.1	-12 ± 26	0.004
HOMA _{IR} score		1.56 ± 0.67	1.25 ± 0.52	-14 ± 26	0.003

Values are means ± SD.

FIGURE 1

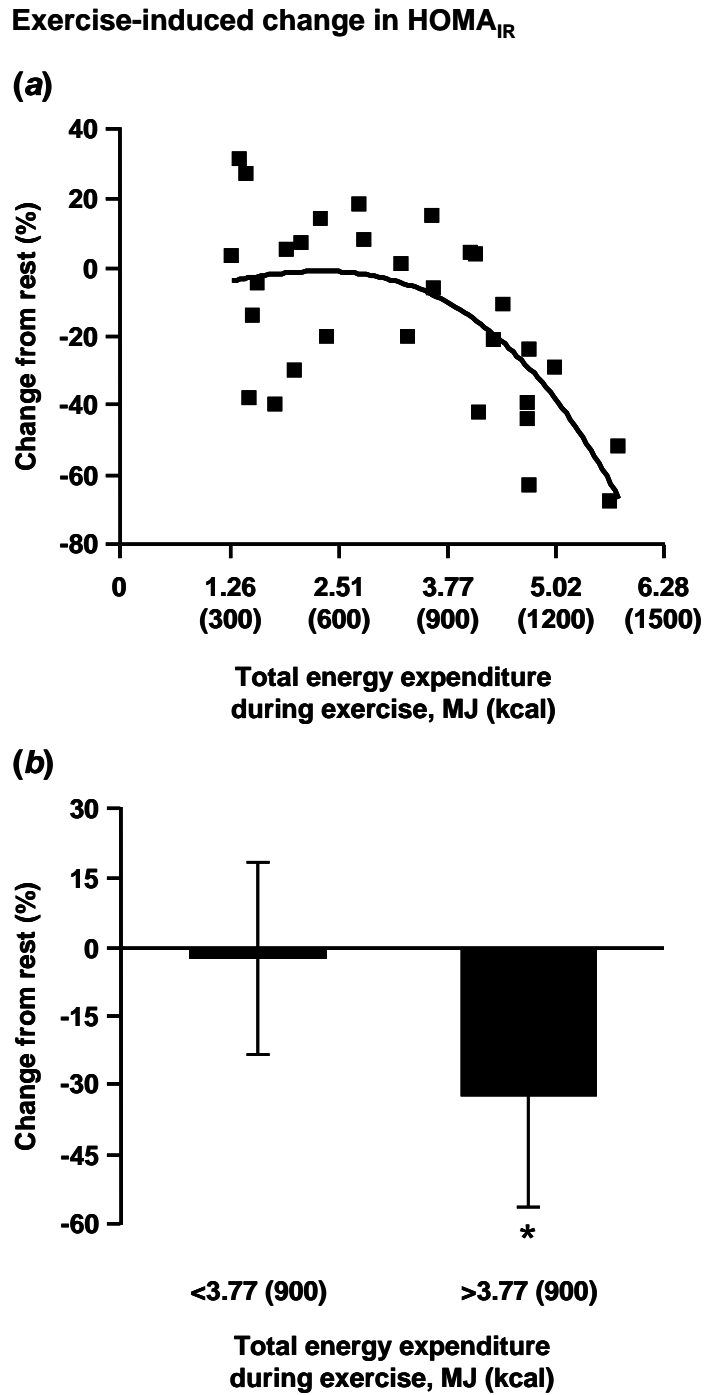


FIGURE 2

